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Specific Features of Alkylation of Organic Hydroperoxides with Chlorinated Hydrocarbons in Superbasic Media

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Abstract—Alkylation of organic hydroperoxides with chlorinated hydrocarbons in superbasic media (dipolar nonhydroxyl solvent–strong ionic base) was performed.

Organic peroxides find increasing use as models and objects in studying numerous basic problems of natural science. Therefore, it is of interest to find new, more convenient synthetic routes to them. For this purpose, it is suggested to use superbasic media consisting of a dipolar nonhydroxyl solvent and a strong ionic base. Such media promote nucleophilic reactions.

We briefly reported previously that the use of superbasic media [hexamethylphosphoramide (HMPA)–alkali metal hydroxide] significantly improves synthesis of organic peroxides by alkylation of hydroperoxides (in particular, cumene hydroperoxide) with haloalkanes [1].

This well-known reaction [2, 3] under "traditional" conditions occurs within several tens of hours, with the yields of dialkyl peroxides being poor [3]. Furthermore, the process involves two preparative steps: synthesis of the hydroperoxide salt and alkylation of ROOM (M = Na, K), with each step requiring appropriate conditions.

With superbasic media (dipolar nonhydroxyl solvent–strong ionic base), it appears feasible to combine both steps in a one-pot synthesis, with improvement of the synthesis parameters and shortening of the reaction time. Further advantages of this procedure as applied to preparation of dialkyl peroxides are higher purity of the target products, simplicity of their isolation, and safety of the process as a whole. The synthesis can be schematically described by Eq. (1).

$$\mathrm{ROOH} + \mathrm{R'X} \xrightarrow[-\mathrm{MX},\ \mathrm{H_2O}]{\mathrm{MOH/HMPA,\ 298\ K}} \mathrm{ROOR'}. \qquad (1)$$

This work continues our studies of specific features of alkylation of hydroperoxides with halogenated hydrocarbons in superbasic media of the above composition.

First, we extended the range of reagents used. Among hydroperoxides, we used cumene hydroperoxide **I**, *tert*-butyl hydroperoxide **II**, and 1-(1-methyl-1-*tert*-butylperoxyethyl)-4-(1-hydroperoxy-1-methylethyl)benzene **III**. The alkylating agents were 1-chlorohexane (HexCl) and benzyl chloride (BnCl). As superbasic medium, in most experiments we used HMPA–NaOH, which provides better results in alkylation of hydroperoxides, compared to the related system with KOH.

The results of this experimental series are given in Table 1. These data show that alkylation with chlorohexane in HMPA–NaOH (system nos. 1–4) is fairly efficient. For example, with HexCl as alkylating agent the yield of dialkyl peroxides was 40–70% or even higher. The previously known procedures for alkylation of hydroperoxides with chlorides do not ensure the yields of dialkyl peroxides higher than 15–30% [2–4]. Therefore, major attention was given to alkylation with bromides, which are less available and more expensive than chlorides. The efficiency of superbasic systems dipolar nonhydroxyl solvent–strong ionic base in alkylation of hydroperoxide **I** with bromide was reported in [1]. The same paper also reported that the yield of dialkyl peroxides in alkylation of **I** with HexCl in HMPA–alkali was as low as 20%. However, improvement of the procedure for isolation of the reaction products allowed the yield to be increased to 46–51%.

One more advantage of chloroalkanes should be noted: whereas bromides are partially hydrolyzed [1], chlorides give virtually no by-products. In particular, with HexCl no 1-hexanol (hydrolysis product) was detected. For both HexCl and BnCl, a clear correlation was observed between the consumptions of the hydroperoxide and chlorinated hydrocarbon.

Since hydroperoxides in the superbasic medium HMPA–NaOH take part in alkylation only, the initial

Table 1. Alkylation of hydroperoxides in the superbasic medium HMPA–NaOH (30 ml of HMPA, 298 K)

System no.	Composition	Amount, mol			$v_0 \times 10^3$, mol l^{-1} s^{-1}	Conversion, %[a]	τ, min	Yield, %[b]
		ROOH	R'Cl	NaOH				
1	**I**–1-HexCl–NaOH	0.01	0.01	0.010	0.10	68 (70)	120	51
2	**I**–1-HexCl–NaOH	0.01	0.015	0.015	1.50	63 (95)	60	46
3	**II**–1-HexCl–NaOH	0.01	0.015	0.015	0.61	70 (88)	120	45
4	**III**–1-HexCl–NaOH	0.01	0.015	0.015	1.50	60 (93)	60	74
5	**I**–BnCl–NaOH	0.01	0.01	0.010	0.61	80 (86)	90	10
6	**I**–BnCl–NaOH	0.01	0.015	0.015	0.70	65 (100)	60	5
7	**II**–BnCl–NaOH	0.01	0.015	0.015	0.07	60 (45)	210	9

[a] Without parentheses, halogenated hydrocarbon; in parentheses, hydroperoxide. [b] Yield of dialkyl peroxide.

rate of consumption of hydroperoxides and their salts (v_0) be considered as a kinetic parameter of the alkylation process. Comparison of the initial rates allows the hydroperoxides to be ranked in the following order with respect to the reactivity: **III** ≈ **I** > **II**.

It is quite natural that the kinetic parameters obtained for hydroperoxides **III** and **I** are virtually equal, since compound **III** can be actually considered as a substituted cumyl hydroperoxide, behaving similarly to **I** in reactions that do not involve the peroxy group. The difference between hydroperoxides **I** and **II** is attributable in part to the somewhat higher acidity of **I** [2]: pK_a 12.6 and 12.8, respectively. It should be noted that these acidity constants refer to aqueous solutions. Apparently, in dipolar nonhydroxyl solvents the difference between the acidities of these hydroperoxides will be more significant.

In contrast to HexCl, in alkylation with BnCl the yields of dialkyl peroxides were low. Furthermore, large amounts of benzaldehyde and of the alcohol corresponding to the hydroperoxide taken were detected.

To account for the different results obtained in alkylation of hydroperoxides in the chosen superbasic medium with HexCl and BnCl, let us consider the sequence of possible transformations (2)–(7). The reaction of a hydroperoxide with an alkali initially gives a salt, which dissociates under the action of a solvent (S) and proton-donor components. Formation of a salt ROOM and its dissociation in the system hydroperoxide–superbase were studied in detail and were described in [5].

$$\mathrm{ROOH + MOH \rightleftarrows ROOM + H_2O}, \qquad (2)$$

$$\mathrm{ROOM + S + HOOR \rightleftarrows ROO^-\cdots HOOR + M^+\cdots S}, \qquad (3)$$

$$\mathrm{ROOM + S + H_2O \rightleftarrows ROO^-\cdots H_2O + M^+\cdots S}, \qquad (4)$$

$$\mathrm{ROOH + OH^- \rightleftarrows ROO^- + H_2O}, \qquad (5)$$

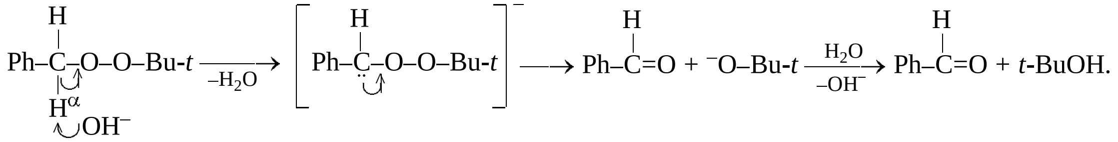
$$\mathrm{ROO^-\cdots HOOR + S \rightleftarrows ROO^- + ROOH\cdots S}, \qquad (6)$$

$$\mathrm{ROO^-\cdots H_2O + S \rightleftarrows ROO^- + HOH\cdots S}. \qquad (7)$$

Since no dialkyl peroxides are formed under the similar conditions but without alkali, the peroxy anion can be considered as a key agent in alkylation of hydroperoxides with a haloalkane [reaction (8)]:

$$\mathrm{ROO^- + R'Cl \longrightarrow ROOR' + Cl^-}. \qquad (8)$$

The low yields of organic peroxides in HMPA–NaOH with BnCl as alkylating agent are due to the nature of the products formed. In particular, a specific feature of such dialkyl peroxides is the presence of labile hydrogen atoms in the α-position relative to the peroxy group. There are indications in the literature that such peroxides decompose under the action of nucleophiles to give the corresponding alcohol and aldehyde [6]. In the system **II**–BnCl–HMPA–NaOH, among the reaction products we also detected benzaldehyde and *tert*-butanol. Their accumulation in the superbasic system suggests realization of this decomposition pathway in our case also [scheme (9)]:



$$\mathrm{Ph{-}\overset{H}{\underset{H^{\alpha}\;\;OH^-}{C}}{-}O{-}O{-}Bu\text{-}\mathit{t}} \xrightarrow[-H_2O]{} \left[\mathrm{Ph{-}\overset{H}{\ddot{C}}{-}O{-}O{-}Bu\text{-}\mathit{t}}\right]^- \longrightarrow \mathrm{Ph{-}\overset{H}{C}{=}O + {}^-O{-}Bu\text{-}\mathit{t}} \xrightarrow[-OH^-]{H_2O} \mathrm{Ph{-}\overset{H}{C}{=}O} + \mathit{t}\text{-}\mathrm{BuOH}. \qquad (2)$$

Table 2. Solvent effect on alkylation of hydroperoxide **I** with hexyl chloride (amounts of **I**, HexCl, and NaOH 3 mmol each; solvent volume 15 ml; 323 K)

Solvent	*DN*	$v_0 \times 10^3$, mol l^{-1} s^{-1}	Conversion, %[a]	τ, min	Yield, %[b]
HMPA	38.8	0.71	68	90	51
DMF	26.6	0.04	73	90	42
Trimethyl phosphate	23.0	0	2	120	0
Propylene carbonate	15.1	0	0	120	0

[a] Hydroperoxide **I**. [b] Yield of dialkyl peroxide.

Apparently, the high rate of decomposition of the forming peroxide prevents its accumulation in the superbasic medium. Since decomposition of the peroxide is a secondary process, there will be a certain delay in accumulation of benzaldehyde and *tert*-butyl alcohol. Similar transformations occur in the system with cumene hydroperoxide. Furthermore, the dialkyl peroxide prepared from **I** and BnCl decomposes by reaction (9) more readily, as suggested by comparison of the amounts of the converted ROOH and formed ROOBn.

We believe that the possibility of reaction (9) should also be taken into account with alkyl peroxides containing an *n*-alkyl radical. However, such peroxides should decompose much more difficultly, since the α-hydrogen atoms in them are less active. For example, about 20% of dialkyl peroxide decomposed in system no. 1, whereas in system no. 2 (with excess alkali) the fraction of the decomposed peroxide was considerably higher.

Our results allow an important conclusion: In synthesis of dialkyl peroxides by alkylation of hydroperoxides with halogenated hydrocarbons containing labile α-hydrogen atoms, the alkali should be taken in an equimolar amount.

Table 3. Experimental and calculated [Eq. (10)] rates of alkylation of hydroperoxide **I**

N(HMPA)	*N*(DMF)	$\log v_0$(HMPA–DMF)	
		experiment	calculation
1	0	–3.158	–3.158
0.86	0.14	–3.328	–3.332
0.64	0.36	–3.602	–3.604
0.47	0.53	–3.810	–3.815
0.31	0.69	–4.013	–4.013
0.20	0.80	–4.185	–4.150
0.06	0.94	–4.328	–4.323
0	1	–4.398	–4.398

To sum up, one more conclusion can be made: Superbasic media (dipolar nonhydroxyl solvent–strong ionic base) are efficient tools in alkylation of hydroperoxides with haloalkanes, allowing the use of chloroalkanes as alkylating agents instead of more reactive but less available bromoalkanes.

The next step of our study was examination of the effect of the solvent on alkylation of **I** with HexCl in the presence of NaOH. For this purpose, along with HMPA, we tested dimethylformamide (DMF), trimethyl phosphate, and propylene carbonate. The results are listed in Table 2. It is seen that hydroperoxide **I** is alkylated only in HMPA and DMF. In the other solvents, no accumulation of dialkyl peroxides was observed in 2 h.

We found that alkylation in HMPA and DMF occurs by similar mechanism. This is indicated, in particular, by the results of alkylation of **I** with 1-chlorohexane in the binary solvent HMPA–DMF (Table 3). The calculated initial rates of the process in the binary solvent were determined by Eq. (10):

$$\log v_0(\text{HMPA–DMF}) = N(\text{HMPA})\log v_0(\text{HMPA}) + N(\text{DMF})\log v_0(\text{DMF}), \quad (10)$$

where $v_0(i)$ are the alkylation rates in individual solvents i and $N(i)$ are the mole fractions of solvents i in the binary solvent.

As seen, the experimental and calculated values of $\log v_0$(DMF–HMPA) are very close.

The fact that alkylation of the hydroperoxides in the presence of MOH in HMPA and DMF occurs only is primarily due, in our opinion, to the specific solvating properties of these solvents. These solvents are strong electron pair donors; therefore, they efficiently solvate cations. However, they do not act as hydrogen bond donors, since their C–H bonds are insufficiently polar. Specifically these features of solvation with dipolar nonhydroxyl solvents provide accumulation in the reaction medium of strong nucleophiles, virtually nonsolvated peroxy anions. For example, peroxy anions formed upon addition of a hydroperoxide to a superbasic medium give complexes with hydroxy compounds (in our case, with nondissociated hydroperoxide and water). This significantly decreases their reactivity; we observed such an effect in oxidation of dimethyl sulfoxide with peroxy anions in a superbasic medium, when water was added to the reaction system [7]. At the same time, dipolar nonhydroxyl solvents also form hydrogen bonds with such hydroxy compounds. Therefore, the presence of such solvents shifts the equilibrium toward formation of weakly solvated peroxy anions. Under such conditions, their concentration is apparently low. However, their high nucleophilicity ensures fast alkylation on adding haloalkanes. The consumption of haloalkanes shifts the equilibrium toward accumulation of new weakly solvated peroxy anions and further accumulation of dialkyl peroxides at high rates by the ionic mechanism.

At the same time, as seen from Table 2, not all the dipolar nonhydroxyl solvents favor alkylation of hydroperoxides with halogenated hydrocarbons. In particular, in trimethyl phosphate and propylene carbonate, no dialkyl peroxide is formed. An empirical semiquantitative characteristic of nucleophilic properties of solvents is the donor number (*DN*) [8]. Experimental data show that only dipolar nonhydroxyl solvents with relatively high *DN* ensure high reaction rates. In HMPA, which has one of the highest donor numbers, alkylation of hydroperoxides occurs considerably faster than in DMF whose electron-donor power is lower. Furthermore, the yield of dialkyl peroxide in HMPA–NaOH is also lower than in DMF–NaOH. Similar trends are observed in other nucleophilic substitutions, in particular, in alkylation of alkali metal carboxylates with haloalkanes [9]. At the same time, no correlation was revealed between the initial reaction rate and other parameters of the solvents used (dielectric permittivity, polarity, polarizability).

Thus, the decisive factor ensuring high rates of alkylation of hydroperoxides with halogenated hydrocarbons and high yields of dialkyl peroxides in the presence of strong ionic bases is the high nucleophilicity of the solvent.

EXPERIMENTAL

Alkylation of hydroperoxides with halogenated hydrocarbons was performed in a temperature-controlled cell at 298 K. The cell was charged with alkali ground under argon and with the purified solvent. This mixture was kept at the required temperature for 30 min, after which the hydroperoxide and, 1 min later, the purified haloalkane were added. The moment of adding the haloalkane was considered as the start of the reaction. The reaction kinetics was monitored by taking samples at regular intervals and analyzing them by iodometric titration for the total content of the hydroperoxide and its salt. As the kinetic criterion we used the initial rate v_0, which was determined by graphic differentiation of the experimental kinetic curve of the consumption of the hydroperoxide and its salt. Experiments showed that v_0 is comparable with the rate of dialkyl peroxide accumulation, which was determined by HPLC according to [10]; therefore, v_0 can be considered as alkylation rate to a full measure. Also, the reaction progress was monitored by GLC (consumption of haloalkane, accumulation of transformation products of reagents and dialkyl peroxides).

The reaction products were isolated after stirring for 60–120 min. To do this, 5 ml of distilled water was added to 15 ml of the reaction mixture, and the mixture was treated with hexane (5 × 5 ml). The hexane extract was washed with water (3 × 5 ml) and dried for 24 h over anhydrous Na_2SO_4. Then the solvent and unchanged haloalkane were distilled off in a vacuum. The dialkyl peroxides obtained were identified by ^{1}H NMR spectroscopy at the Institute of Organic Chemistry, National Academy of Sciences of Ukraine.

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